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The Use of Neuropeptide Y as a Measurement of the Effectiveness of Stress Inoculation

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Post-traumatic stress disorder and other stress-related illnesses constitute a large number of casualties in the United States Army. To prevent the performance-degradation effects of stress, the concept of stress inoculation develops, which allows for the development of stress resilience through the gradual introduction of stressors. Comprehensive Soldier Fitness is one stress inoculation program developed by the Army. However, its effectiveness is unproven. One way to measure a person?s resilience to stress is through their circulating concentration of neuropeptide Y, which has been linked to the prevention of stress-related effects. We propose an experiment to determine the effectiveness of the Comprehensive Soldier Fitness program by determining if Soldiers that have received the training exhibit a higher spike in neuropeptide Y during high-stress events.

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ABSTRACT

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Introduction

Over the course of their lives, approximately half of all adults in the United States experience a traumatic event. However, only five to ten percent of people in the United States will experience any form of long-term issues from that event. This is known as posttraumatic stress disorder (Ozer & Weiss, 2004). In order to properly examine why only a small percentage of those that experience a traumatic event develop a psychological disorder from it, we must first define the relevant terms.

The definition of PTSD requires a clarification of what exactly constitutes a traumatic event. Some people may experience certain events as traumatic, while others exposed to the same event may find it mundane. For example, a police officer encountering a severed limb at the scene of a crime will not have the same experience as a child that encounters the same severed limb on a playground. Ozer and Weiss (2004) acknowledge the standard definition of a traumatic event as one that involves immediate horror and threat to survival, such as events experienced in war or large-scale, tragic events such as natural disasters. Acknowledging the differing reactions in different people to similar events, Ozer and Weiss (2004) expand their definition to include highly distressing events that may not evoke the same response as immediate life-threatening events. They propose that the key identifier for a traumatic event should be the presence of central nervous system arousal at the time of the event. This definition accounts for the differing circumstances that determine whether a given person experiences a certain event as traumatic or not.

Now that a framework for determining whether an event is traumatic has been established, we must address the issue of PTSD. Posttraumatic stress disorder, in its current incarnation, has a relatively short history, first appearing as a diagnosis in the American

Psychiatric Association's third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, DSM-III, in 1980 (Scott, 1990). However, its history can be traced back to the descriptions of combat stress reactions of Soldiers in the 18th century by military surgeons (Jones, 1995). In modern records, remarkably similar maladies are mentioned in the DSM-I. In the first edition, this was known as "gross stress response," and was a result of combat studies done during the Second World War. Since 1952, the disorder has evolved to become what it is today, due primarily to more comprehensive studies completed in the wake of the United States' involvement in the Vietnam War (Scott, 1990).

In the current edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders*, DSM-IV-TR (2000), posttraumatic stress disorder is defined as "the development of characteristic symptoms following exposure to an extreme traumatic stressor." These symptoms include negative recollections of the event, the avoidance of stimuli associated with the trauma in question, and persistent feelings of anxiety or increased arousal.

Background

PTSD

Psychological casualties have a long history with the United States military. The stresses of war can place a huge psychological burden on Soldiers that are often not trained or incapable of handling them. In the Second World War there was, on average, one psychiatric casualty for every four physically wounded casualties. At Guadalcanal in particular, numbers were even higher, with forty percent of casualties evacuated from the battlefield suffering from "disabling neuromental disease" (Marlowe, 2001). At the time, PTSD was not well understood, and casualties were attributed to "battle fatigue." Soldiers that were evacuated due to battle fatigue

rarely recovered sufficiently to return to duty, while those that were treated in forward areas and expected to return to duty often recovered enough to continue fighting (Lukey & Tepe, 2008).

We saw a similar situation in Vietnam. Vietnam was different from World War II, as there was a higher rate of psychiatric casualties for those involved in the war after the intense combat began to die down. Studies done after the war showed a 4% PTSD rate in veterans that had not been wounded, while wounded veterans had a 20% PTSD rate (Helzer, Robins & McElvoy, 1987). Many of the Soldiers in the war were not career Soldiers, but draftees, and they brought their problems home with them after the conclusion of the war. A study conducted by Figley and Nash (2007) on Vietnam veterans suggested that PTSD is associated with premature mortality, from both external and internal causes. Of course, this is a problem, as the Army wants to preserve the lives of its Soldiers. The issue of PTSD did not resurface in any significance among United States Soldiers again until the Gulf War.

As commanders become more aware of the issue of psychiatric casualties in the military, measures have been emplaced in order to both identify Soldiers that have developed or are at risk for PTSD, as well as to mitigate the risk of Soldiers developing PTSD. The treatment of psychiatric casualties has played an important role in the United States military in recent years, especially since the start of the campaigns in Afghanistan and Iraq.

Many of the problems stemming from the current war are due to the expectation of combat. This effect was observed in the Vietnam War, where the majority of psychiatric casualties occurred after the period of most intense combat had passed (Hyams, Wignall & Roswell, 1996). In the current war, the nature of low-intensity conflict lends itself to a higher rate of PTSD development than would a high-intensity conflict. Soldiers involved in the current conflicts experienced only a brief period of intense combat at the beginning of combat

operations, yet an unexpected number of Soldiers involved have developed PTSD. This may be due in part to the effect of stress anticipation on the level of stress experienced. Because there is no clearly-defined front line in Iraq and Afghanistan, Soldiers that do not normally have a direct combat role may find themselves in the midst of battle due to the unpredictable nature of insurgent attacks (Hoge, Castro, Messer, McGurk, Cotting, & Koffman, 2004).

Numerous studies show that anticipation of a stressful event plays a significant role in the actual level of stress experienced. Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson (2006) demonstrated that, when stress is certain to occur, emotional reactions mimic the responses that occur in response to stress. It is theorized that the expectation of stress prepares the body for stress by evoking an early response to the stressor that enhances the body's ability to cope with the stressor to follow. By contrast, low or no expectation of stress does not result in the corresponding increase in emotional response, so the body experiences a greater stress reaction than if it had been prepared through expectation of stressors. This certainly applies to today's conflicts, as non-combat arms Soldiers may not expect to find themselves in direct contact with the enemy and thus are not primed for the stress reaction that occurs in the heat of battle.

The high stress of combat may result in decreased Soldier performance. Therefore, it follows that a reduced stress response will lead to better combat effectiveness. The Yerkes-Dodson curve demonstrates how human performance changes in reaction to differing levels of stress (Yerkes & Dodson, 1908). The curve takes the shape of an inverted "U," with level of arousal on the x-axis and level of performance on the y-axis. The curve demonstrates that there is a certain level of arousal that can be achieved in order to attain the highest possible level of

performance. However, arousal levels that lean too far to one side or the other of the spectrum results in a non-optimum level of performance.

For simple tasks, the level of arousal correlates positively with an increase in performance. Complex tasks, such as combat, are different. As arousal increases, performance increases until the maximum possible level of performance is reached, at which point performance begins to rapidly decrease as more stress is added. A low level of stress creates a low level of arousal, resulting in Soldiers often feeling bored and being inattentive; however, as arousal increases, Soldiers then become attentive, as they are required to attend to the situation around them in order to be successful. Further arousal then begins to decrease Soldiers' performance, as they become unable to focus or effectively attend to the situation at hand. This inability to focus may result in mission failure. The implications of the Yerkes-Dodson (1908) law are well-documented, and numerous studies reinforce the idea that some level of stress is required for optimal performance, but reaching too far beyond that level leads to performance degradation.

One way to increase the performance of Soldiers under extreme stress is through stress resilience training, known as stress inoculation. Stress inoculation is the idea that exposing trainees to an intensely stressful situation will allowing them to acclimate to increased stress, thus enabling them to perform more effectively in similar, real-world situations. Some researchers suggest additional steps, such as the teaching of coping mechanisms prior to the beginning of introducing stressors (Meichenbaum, 1996). However, the goal of stress inoculation remains the same: to push the peak of the Yerkes-Dodson (1908) curve to the right, allowing for a longer buildup of performance before the Soldier is overwhelmed by stress and begins to exhibit degraded performance. We hypothesize that training Soldiers in controlled, high-stress

environments for extended periods of time will have the effect of moving the peak of the Yerkes-Dodson (1908) curve further down the spectrum of stress, so that Soldiers can operate more effectively in high-stress environments such as what they will experience in combat. By this definition, Comprehensive Soldier Fitness is a stress inoculation program.

The United States Army relies on stress inoculation as its primary method for training Soldiers for the stresses of combat. The military espouses a "train as you fight" mentality, with the assumption that realistic training can properly simulate the stresses of combat. Nearly all military training programs, including basic training and ranger school, follow the pattern of introducing low-intensity stressors at first, followed by progressively more intense stressors with the intention of inoculating trainees to the high levels of stress that they will undoubtedly experience in combat.

Few laboratory studies examine the effects of stress inoculation, but the available evidence is in favor of its utility as a performance-enhancing measure. Beilock, Kulp, Holt & Carr (2004) demonstrated the effectiveness of stress-inoculation on working memory tasks. When participants were frequently trained to perform mathematical problems under high levels of performance pressure, they performed much better when tested under pressure than those with less or no training under performance pressure.

In a physical performance study, Beilock & Carr (2001) found that golfers trained to putt under audience observation performed equally as well as golfers trained under no observation in a low-stress putting task. However, under high-pressure conditions, simulated by a large monetary prize, the golfers trained under audience observation performed significantly better than those who were not trained under audience observation.

The aforementioned studies suggest that stress inoculation, when properly applied is, in fact, effective in mitigating undesirable stress responses in people in high-stress environments. However, it is not always possible to place Soldiers in a high-stress combat situation in order to determine whether their previous stress-inoculation training was effective. Therefore, a biological measure must be selected in order to determine, in advance, whether a training task designed to inoculate trainees against stress is, in fact, effective.

Yet while the stresses that are associated with combat typically inflict negative side effects, positive experiences can be drawn from them. Such phenomenon has been termed posttraumatic growth. According to Tedeschi, Calhoun, and Park (1998), posttraumatic growth is based on the idea that stress and trauma can bring about positive personal transformations within a person even though he or she suffers distress. The transformations and growth processes that researchers have seen are typically categorized into three main areas: strength through suffering, existential reevaluation, and psychological preparedness (Janoff-Bulman, 2006). Based on this concept, stressors and traumatic events such as war and life-threatening illnesses, may create opportunities through which people can improve psychologically (Elder & Clipp, 1989; Heffernon, Grealy, & Mutrie, 2009).

In order to better quantify the different characteristics and qualities that people report as improving in the wake of a stressful event, several methods were developed to model posttraumatic growth. One leading method for assessing posttraumatic growth was developed by Tedeschi and Calhoun (1996). They developed the Posttraumatic Growth Inventory and is comprised of 21 questions pertaining to five distinct factors: Relating to Others, New Possibilities, Personal Strength, Spiritual Change, and Appreciation for Life. The benefits of this model are that it has internal consistency, acceptable test-retest reliability, and displays an

approximately normal distribution of scores based on a variety of traumatic experiences. A second method for the assessment of posttraumatic growth is the Stress-Related Growth Scale. Park, Cohen, and Murch (1996) developed the SRGS to examine the areas of positive changes in personal resources, social relationships, and coping skills. The SRGS is comprised of 50 questions and has adequate test-retest and internal reliability, as well as scale validity.

A number of studies show the prevalence of posttraumatic growth. Sledge, Boydstun, and Rabe (1980) found that 61.1% of U.S. Air Force personnel shot down over North Vietnam during the Vietnam War viewed their imprisonment as an experience from which they benefited psychologically. Another study of former Israeli POWs of the Yom Kippur War found that ex-POWs "endorsed more growth than the combat veterans on all the posttraumatic growth subscales" (Solomon & Dekel, 2007). They suggest that posttraumatic growth is influenced by a combination of the harshness of the experience and the suffering that the POWs endured. Maercker and Zoellner (2004) also conducted a study on former political prisoners held in East Germany before the fall of the Berlin Wall. In their study, the former prisoners were subjected to months of "physical and psychological torture," yet 72% of the subjects reported one or more examples of posttraumatic growth from the experience (Maercker & Zoellner, 2004).

While positive outcomes may result from traumatic events, posttraumatic growth is not an indication of high resilience. As Levine and colleagues explain, posttraumatic growth is "inversely associated" with resilience (Levine, Laufer, Stein, Hamama-Raz, & Solomon, 2009). Their research, conducted on civilians exposed to acts of terror and combat experienced Soldiers, indicates that people who have higher resiliency tend to suffer less psychologically and therefore have less opportunity for posttraumatic growth. Conversely, people who are less resilient tend to be more susceptible to suffering from traumatic experiences and can in turn grow from them.

The inverse relationship between posttraumatic growth and resiliency generates the need for new methods to be able to measure and understand the causes of resilience.

Neuropeptide Y

Neuropeptides are amino acids that act as neurotransmitters within the brain, passing signals from one neuron to another. Every neuropeptide influences the brain in a particular way, and are involved in processes such as learning, eating, and the sensation of pain. One particular neuropeptide of interest is neuropeptide Y (NPY).

NPY is a peptide of the pancreatic polypeptide family found in extremely high concentrations in the central nervous systems of mammals, most prevalently in the cortical, limbic, and hypothalamic regions of the mammalian brain (Allen, Adrian, Allen, Tatemoto, Crow, Bloom, & Polak, 1983). One of the roles of NPY is related to eating behavior. Clark, Kalra, Crowley, & Kalra (1984) found that human pancreatic NPY, injected into rats, resulted in the rats consuming three times their normal food intake, suggesting that it plays a significant role in the neural regulation of the feeding behavior of mammals. Since this study, high levels of NPY have been linked to obesity in human populations, due to its effect on increased food intake and decreased physical activity.

NPY has another effect, one that acts on the sympathetic nervous system and is quite unrelated to feeding, that makes it a highly desirable measure for determining a metric that will quantitatively measure human resilience to stress. When people are placed into stressful situations, the body's natural response is to activate the sympathetic nervous system (SNS). Responsible for generating the body's "fight or flight" response, the sympathetic nervous system is primarily involved in increasing heart rate and blood pressure and mobilizing energy stores for immediate use (Lundberg, 2000). While such a biological response is necessary for quickly

responding to stressful situations, over-stimulation of the SNS can create problems. Cohen, Janicki-Deverts, & Miller (2007) notes that prolonged SNS activation can cause feelings of anxiety and depression, and that chronic exposure can result in long-term changes in physiological responses to stress. However, research indicates that there is an optimal range of SNS activation that results in enhanced performance (Dienstbier, 1991).

The explanation for why an optimal range of sympathetic nervous system activation exists is due to two neurotransmitters that are released into the blood stream, norepinephrine (NE) and neuropeptide Y (Zukowska-Grojec, 1995). According to a review of neurobiological studies by Southwick, Bremner, Rasmusson, Morgan, Arnsten, & Charney (1999), higher levels of NE can lead to potentially performance-degrading biological changes, like increased heart rate, blood pressure, anxiety, and panic. Additionally, significantly higher baseline levels of NE have been found in patients with PTSD than in those without PTSD (Geracioti, Baker, Ekhator, & West, 2001). As the research indicates, high quantities of norepinephrine in the bloodstream can be detrimental to stress regulation and performance in stressful situations. Yet the negative effects that accompany high levels of NE are offset by the release of NPY into the blood. Part of the method by which NPY prevents excess levels of NE is through simply inhibiting its continued release (Southwick et al., 2008). NPY's ability to contain the amount of NE in the blood helps to keep the SNS activation within the optimal performance range (Zukowska-Grojec, Dayao, Karwatowska-Prokopczuk, Hauser, & Doods, 1996).

Further illustration of the inverse relationship between norepinephrine and NPY, and the effects that they have on the regulation of stress and behavior can be seen in a range of various experiments. Studies conducted on rats found a correlation between the level of stress experienced and the level of circulating NPY, as well as the stress-protection effects of NPY

(Castagne, Corder, Gaillard, & Mormede, 1987; Heilig & Murison, 1987; Husum & Mathe, 2002; Thorsell, Svennson, Wiklund, Sommer, Ekman, & Heilig, 1998; Thorsell, Michalkiewicz, Dumont, Quirion, Caberlotto, Rimondini, Mathe, & Heilig, 2000). Since this research, similar effects have been observed in humans (Morgan, Wang, Rasmusson, Hazlett, Anderson, & Charney, 2001). A series of studies that are of particular interest have found similar results in Soldiers during the course of a military survival school (Morgan, Wang, Southwick, Rasmusson, Hazlett, & Hauger, 2000, 2002). The researchers collected blood samples both before and after training in order to determine the levels of NPY and NE that were released. These levels were then compared to the Soldier's behavioral performance under stress to see if higher levels of either neurotransmitter had an effect on coping with the situation. The results of these studies indicate that Soldiers who performed well during stressful situations had significantly increased NPY levels and experienced less psychological distress. Similarly, Yehuda, Brand, and Yang (2006) found that veterans without PTSD had significantly higher NPY levels than similar veterans with PTSD. Additionally, they found that NPY levels were predictive of the extent of PTSD symptom improvement, with higher NPY levels resulting in greater improvements. Sajdyk, Johnson, Leitermann, Fitz, Dietrich, Morin, Gehlert, Urban, & Shekhar (2008), examined the administration of NPY into the basolateral nucleus of the amygdala. The resultant observations indicate that the researchers were able to produce selective stress-resilient behavioral responses and that such resilient behaviors were present for up to 8 weeks after the administration of NPY.

These studies suggest that NPY is an effective metric for measuring stress resilience. Fortunately, the measurement of NPY concentration within the bloodstream is not particularly

difficult, requires little in the way of specialized equipment, and can be performed in most field conditions.

Since NPY is circulated throughout the bloodstream, samples can be collected in the field by way of venipuncture on a participant's forearm. The only personnel required in the field is anyone qualified to draw blood. Since medics are often assigned to units in training, they can collect the samples. The blood samples are collected in Vacutainer tubes and placed in an ice bath to prevent the degradation of proteins. The samples can be stored in the ice bath until they can reach a lab for analysis. Once the samples get to a lab, they are separated into plasma, after which they can be analyzed using specialized NPY analysis kits that measure the concentration of NPY within a given sample (Institute for Clinical and Translational Science [ICTS], 2010).

Proposed Study Method

The proposed study would be conducted in conjunction with the Army's Comprehensive Soldier Fitness (CSF) program to determine the effectiveness of stress resilience training in increasing the levels of neuropeptide Y when Soldiers are exposed to combat.

Participants

In accordance with the CSF program's assessment plan, this study will rely on the participation of a smaller sample of Soldiers from within the CSF assessment brigades. Approximately one hundred Soldiers from each of the contributing CSF brigades will be asked to volunteer for this physiological assessment. These Soldiers will be randomly selected based on whether or not they have completed the subjective assessment phase of the CSF program. The participants should be a representative sample of the Army population. The objective is to secure the voluntary participation of 50 Soldiers who completed portions of the CSF training program and 50 Soldiers who have not.

Due to the voluntary nature of this phase of the CSF assessment program, all Soldiers will be treated in accordance with the ethical standards of the American Psychological Association. As such, this experiment will be conducted after approval from the U.S. Army's Human Subjects Committee.

Apparatus

This study requires that blood be drawn and analyzed for the presence and concentration of neuropeptide Y. As such, specialized equipment will be required. On-site, researchers will require pre-chilled, lavender-topped Vacutainers. The lavender top indicates that these tubes contain EDTA, and anti-coagulant used for whole blood. Aprotinin solution will be required in order to reduce the breakdown of proteins after leaving the bloodstream. Researchers will require an ice bath in which to store the blood samples until they can be brought to a centrifuge capable of at least 1500 g. 12x75mm polypropylene tubes will serve as storage for the plasma samples.

Off-site, researchers will require a way to test for the concentration of neuropeptide Y. Neuropeptide Y can be tested for with an EIA kit designed for that particular neuropeptide. These kits are available from pharmaceutical companies such as Phoenix Pharmaceuticals and RayBiotech. These kits contain the necessary apparatus to test for neuropeptide Y concentration with the exception of some basic laboratory equipment such as pipettes and an orbital plate shaker.

Procedure

The study design is a 2x3 mixed ANOVA. The independent variable is whether or not the participant conducted CSF training prior to undergoing high-stress combat medical training. The dependent variable is the amount of bloodstream neuropeptide Y levels before, during, and one day after a Soldier undergoes the high-stress training. This design will allow us to determine a

base NPY level for each Soldier before undergoing the high-stress training, and compare it to the Soldier's NPY level during and after the event in order to determine if the CSF training did in fact have an effect on the Soldier's long-term resilience to stress.

Researchers will draw blood from both the experimental and control groups before any of the training. This is the baseline to which the following blood samples will be compared. The experimental group will then conduct CSF training. Within one week of the experimental group's completion of the CSF training, both groups of Soldiers will complete a high-stress combat medical training scenario that involves simulated enemy direct fire, indirect fire, and wounded friendly Soldiers. Soldiers will be required to complete combat lifesaver tasks to an exacting standard under difficult time constraints. The goal of the high-stress training is to stress each Soldier heavily enough to elevate the levels of NPY within the bloodstream. Blood will be drawn and prepared for storage during the training exercise. One day after the high-stress training event has concluded, blood will be drawn for each Soldier a final time to determine whether the bloodstream NPY concentration has returned to the baseline level.

Researchers should draw and prepare blood samples in the following manner. At least 3 mL of blood will be drawn from each Soldier's arm and collected into pre-chilled, lavender-topped Vacutainers. Aprotinin solution (150 μL) of will be added to the Vacutainer to prevent degradation of proteins in the blood sample. The samples will be mixed by inversion, and placed in an ice bath to be transported to the centrifuge. The blood samples must be separated using the centrifuge within ten minutes of collection. The centrifuge should be run at 4˚ C for fifteen minutes at 1500 g. This will allow the plasma to separate from the whole blood. Researchers will then transfer the separated plasma into 12x75mm polypropylene tubes and stored at -800˚ C until time of analysis (Phoenix Pharmaceuticals, 2009).

After the conclusion of both the CSF and high-stress training events, researchers will conduct an enzyme-linked immunosorbent assay (ELISA) on each sample to determine the concentration of NPY in the bloodstream. NPY ELISA kits will allow the researchers with basic laboratory equipment to conduct tests to measure the NPY concentration of each sample.

Summary

We hypothesize that Soldiers in both the experimental and control groups should have similar baseline NPY bloodstream concentrations. However, while under stress, the experimental group is expected to exhibit a higher mean NPY concentration than the control group. The final concentration of the sample taken one week after the high-stress training should be equal in both groups, as well as equal to the baseline concentration measured before training. This result will provide evidence that CSF training is indeed effective in increasing the long-term resilience to stress of U.S. Army Soldiers, and that it has the potential to ultimately contribute to a more effective fighting force.

Annotated References

Allen, Y.S., Adrian, T.E., Allen, J.M., Tatemoto, K., Crow, T.J., Bloom, S.R., & Polak, J.M. (1983). Neuropeptide Y distribution in the rat brain. *Science, 221*(4613), 877-879.

This experiment determined that NPY in the rat brain was most highly concentrated in the cortical, limbic, and hypothalamic regions of the brain.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

This manual used in the discipline of psychiatry outlines the definition and symptoms of various psychiatric diseases, one of them being PTSD.

Beilock, S.L., & Carr, T.H. (2001). On the fragility of skilled performance: What governs choking under pressure? *Journal of Experimental Psychology-General,* 130(4), 701-725.

The results showed that golfers trained to putt under audience observation performed equally as well as golfers trained under no observation in a low-stress putting task. However, under high-pressure conditions, golfers trained audience observation performed significantly better than those who were not trained under audience observation.

Beilock, S.L., Kulp, C.A., Holt, L.E., & Carr, T.H. (2004). More on the fragility of performance: Choking under pressure in mathematical problem solving. *Journal of Experimental Psychology-General,* 133(4), 584-600.

This study found that frequently practiced math problems resulted in better performance under pressure than infrequently practiced problems.

Castagne, V., Corder, R., Gaillard, R,. & Mormede, P. (1987). Stress-induced changes of circulating neuropeptide Y in the rat: comparison with catecholamines. *Regulatory Peptides, 19,* 55-63.

This experiment found a correlation between the magnitude of stressors introduced to rats and their corresponding magnitude of NPY.

Clark, J.T., Kalra, P.S., Crowley, W.R., & Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology, 115*(1), 427-429.

This experiment found that a dosage of human pancreatic NPY injected into rats resulted in significantly increased food intake.

Cohen, S., Janicki-Deverts, D., Miller, G. E. (2007). Psychological stress and disease. *Journal of the American Medical Association, 298,* 1685–1687.

This study examines the plausibility of the belief that stress contributes to a variety of disease processes. It is found that there are associations between stress and diseases, such as depression, autoimmune diseases, and wound healing, indicating that stress can increase the likelihood for and intensity of diseases.

Dienstbier, R. A. (1991). Behavioral correlates of sympathoadrenal reactivity: the toughness Model. *Medicine and Science in Sports and Exercise, 23*(7), 846-852.

This study reviews research on increased levels of epinephrine and norepinephrine and performance. This study indicates that higher levels are associated with physiological "toughness" and improved performance in stressful situations and an increased tolerance of stressors.

Elder Jr., G., & Clipp, E. (1989). Combat experience and emotional health: Impairment and resilience in later life. *Journal of Personality, 57*(2), 311-341.

This study examines potential psychological gains in combat veterans from World War 2 and Korea. The research indicates that veterans who experienced heavy combat were at greater risk of emotional and behavioral problems later in life but that they ultimately became more resilient than veterans with less combat exposure.

Figley, C.R. & Nash, W.P. (Eds.). (2007). *Combat stress injury: Theory, research, and management*. New York: Taylor & Francis Group.

This study found a positive correlation between a diagnosis of PTSD and premature mortality.

Geracioti T. D., Baker, D. G., Ekhator, N. N., & West, S. A. (2001). CSF norepinephrine concentrations in posttraumatic stress disorder. *The American Journal of Psychiatry, 158*(8), 1227-30.

This study sought to determine norepinephrine levels in patients with PTSD. The results indicate that norepinephrine concentrations were significantly higher in people with PTSD than in healthy individuals and that norepinephrine levels positively correlate to the severity of PTSD symptoms.

Heffernon, K., Grealy, M., & Mutrie, N. (2009). Post-traumatic growth and life threatening physical illness: a systematic review of the qualitative literature. *British Journal of Health Psycholo*gy, *14,* 343-378.

This study aimed to synthesize qualitative data on PTG and illness related trauma. The research suggest that unique elements of illness related PTG require additional research to fully understand the processes and outcomes of physical illness trauma.

Heilig, M. & Murison, R. (1987). Intracerebroventricular neuropeptide Y protects against stress-induced gastric erosion in the rat. *European Journal of Pharmacology, 137*(1), 127-129.

This experiment found that rats that had been administered a dosage of NPY exhibited less stress-induced gastric erosion that control rats.

Helzer, J.E., Robins, L.N., & McEvoy, L. (1987). Post-traumatic stress disorder in the general population. *New England Journal of Medicine, 317*, 1630-1634.

This study examined the prevalence of PTSD in the general population, to include Vietnam veterans. Vietnam veterans who were wounded had the highest prevalence rates at 20% while the general civilian population rate was 1%. Prevalence rates for civilians who were physically assaulted and Vietnam veterans who were not wounded was 3.5%. Behavioral problems during the early teen years were associated with development of PTSD in those exposed to a traumatic event.

Hoge, C.W., Castro, C.A., Messer, S.C., McGurk, D., Cotting, D.I. & Koffman, R.L. (2004). Combat duty in Afghanistan, mental heath problems, and barriers to care. *The New England Journal of Medicine, 351*(1), 13-22.

The authors indicate that the nature of counterinsurgency warfare may contribute to higher levels of stress among non-combat arms Soldiers, due to their expectation not to find themselves in direct contact with the enemy.

Husum, H. & Mathe, A.A. (2002). Early life stress changes concentrations of neuropeptide Y and corticotrophin-releasing hormone in the adult rat brain. *Neuropsychopharmacology, 27*(5), 756-764.

This study found that rats that had been exposed to high levels of stress in early life exhibited differing levels of NPY than control rats.

Hyams, K.C., Wignall, F.S. & Roswell, R. (1996). War syndromes and their evaluations: from the U.S. civil war to the Persian Gulf War. *Annals of Internal Medicine, 125*(5), 398-405.

The authors found that the majority of psychiatric casualties stemming from the Vietnam War occurred after the periods of most intense combat had passed.

Institute for Clinical and Translational Science. (2010). *Neuropeptide Y sample collection*. Retrieved May 5, 2010, from http://www.icts.uiowa.edu/content/neuropeptide-y-npy-sample-collection.

This document outlines the procedure for the collection of NPY samples from venous blood, and their preparation for analysis.

Janoff-Bulman, R. (2006). Schema-Change Perspectives on Posttraumatic Growth. *Handbook of posttraumatic growth: Research & practice* (pp. 81-99). Mahwah, NJ: Lawrence Erlbaum Associates.

In adding to the study of posttraumatic growth, Janoff-Bulman develops three generalizations in which the majority of posttraumatic growth processes can be categorized: strength through suffering, existential reevaluation, and psychological preparedness.

Jones, F.D. (1995). Traditional warfare combat stress casualties. In F.D. Jones, L.R. Sparacino, V.L. Wilcox, J.M. Rothberg, & J.W. Stokes (Eds.), *War Psychiatry*. Washington, D.C: Borden Institute.

The author found that the descriptions of combat stress reactions from military surgeons in the 18th century were remarkably similar to current descriptions of PTSD and stress reactions.

Levine, S., Laufer, A., Stein, E., Hamama-Raz, Y., & Solomon, Z. (2009). Examining the relationship between resilience and posttraumatic growth. *Journal of Traumatic Stress, 22*, 282-286.

This article examines the interrelationship between resilience and posttraumatic growth through studies conducted on Israeli civilians and Soldiers exposed to terror and war during the second Lebanon War. The research shows high levels of resilience were associated with the least amount of posttraumatic growth.

Lundberg, U. (2000). Catecholamines. In G. Fink (Ed.), *Encyclopedia of stress* (Vol. 1, pp. 408–413). San Diego, CA: Academic Press.

This article highlights the role of the sympathetic nervous system in preparing the body for stressful situations. The SNS prepares the "fight or flight" response which increases the body's heart rate, blood pressure, and mobilization of energy stores for immediate use.

Maercker, A., & Zoellner, T. (2004). The Janus face of self perceived growth: Toward a two-component model of posttraumatic growth. *Psychological Inquiry, 15*, 41–48.

This study examines the possibilities and limitations of Tedeschi and Calhoun's model for assessing posttraumatic growth and presents an investigation into PTG experiences by former political prisoners of East Germany.

Marlowe, D.H. (2001). Psychological and psychosocial consequences of combat and deployment with emphasis on the Gulf War. Santa Monica, CA: RAND Corportaion, MR-1018/11-OSD.

This report discusses the historical impact of war as well as the resurgence of interest in this issue due to the Gulf War.

Meichenbaum, D. (1996). Stress inoculation training for coping with stressors. *The Clinical Psychologist, 49,* 4-7.

The author discusses a three phase program that includes: conceptualization, skills acquisition and rehearsal and application and follow-through that can be used in a variety of stressful situations, whether acute or chronic in nature. This program may be used in individual or group settings and varies in length from 20 minutes to several sessions over a period of several weeks to a year. In the conceptualization phase, individuals learn how to associate stressors with particular goals and how to determine whether or not problem-focused or emotion-focused coping should be applied. In the skills acquisition phase, individuals learn specific coping skills they may employ. Finally in the application and follow-through phase, individuals actually apply what they have learned across various stressor situations.

Morgan, C. A., III, Rasmusson, A. M., Wang, S. Hoyt, G., Hauger, R. L. & Hazlett, G. (2002). Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: Replication and extension of previous report. *Biological Psychiatry, 52*(2), 136-142.

A replication of an earlier study conducted by Morgan III et al. in 2000.

Morgan, C.A., III, Wang, S., Rasmusson, A., Hazlett, G., Anderson, G., & Charney, D.S. (2001). Relationship among plasma cortisol, catecholamine, neuropeptide Y, and human performance during extreme uncontrollable stress. *Psychosomatic Medicine, 63,* 412-422.

This experiment was conducted on Navy personnel under a similar high stress survival exercise and produced similar results. Soldiers who performed better under the stress had higher levels of NPY in their blood.

Morgan, C. A., III, Wang, S., Southwick, S. M., Rasmusson, A., Hazlett, G., & Hauger, R.L. (2000). Plasma neuropeptide-Y concentrations in humans exposed to military survival training. *Biological Psychiatry, 47*(10), 902-909.

An experiment conducted on Special Forces Soldiers who were conducting extreme survival training. Tests showed that the Soldiers had higher-than-normal levels of NPY in their blood while not displaying adverse performance affects.

Nitschke, J.B., Sarinopoulos, I., Mackiwicz, K.L., Schaefer, H.S., & Davidson, R.J. (2006). Functional neuroanatomy of aversion and its anticipation. *NeuroImage, 29*(1) 106-116.

This experiment found that emotional responses when participants believed that stress was imminent was similar to the responses that occur in response to actual stressors.

Ozer, E.J. & Weiss, D.S. (2004). Who develops posttraumatic stress disorder? *Current Directions in Psychological Science, 13*(4), 169-172.

The authors outline statistics involving the development of stress-related disorders and PTSD.

Park, C. L., Cohen, L. H., & Murch, R. L. (1996). Assessment and prediction of stress-related growth. *Journal of Personality, 64*(1), 71-105.

This study reports the development of the Stress-Related Growth Scale and 2 subsequent experiments in which it has been used to determine stress-related positive outcomes. The SRGS specifically categorizes PTG into 5 areas: Intrinsic Religiousness, Social Support Satisfaction, Stressfulness of the Negative Event, Positive Reinterpretation and Acceptance Coping, and Number of Recent Positive Life Events.

Phoenix Pharmaceuticals, Inc. (2009). *Protocol for NPY EIA Kit*. Retrieved from http://www.phoenixpeptide.com/catalog/repository/EIA/EK_049_03.pdf

This document specifies the procedure for analysis of NPY concentration from plasma samples using an NPY EIA kit.

Rasmusson, A. M., Hauger, R. L., Morgan, C. A., Bremner, J. D., Charney, D. S. & Southwick, S. M. (2000). Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biological Psychiatry, 47*(6), 526-539.

This study found that Soldiers with PTSD resulting from combat stress had lower than normal baseline concentrations of NPY.

Sajdyk, T. J., Johnson, P. L., Leitermann, R. J., Fitz, S. D., Dietrich, A., Morin, M., Gehlert, D. R., Urban, J. H., & Shekhar, A. (2008). Neuropeptide Y in the amygdala induces long-term resilience to stress-induced reductions in social responses but not hypothalamic-adrenal-pituitary axis activity or hyperthermia. *The Journal of Neuroscience, 28*(4), 893-903.

This experiment found that NPY within the body can mitigate the social response effects of stress.

Scott, W.J. (1990). PTSD in DSM-III: A case in the politics of diagnosis and disease. *Social Problems, 37* (3), 294-310.

The author details the addition and development of PTSD in the current edition of the DSM.

Sledge, W. H., Boydstun, J. A., & Rabe, A. J. (1980). Self-concept changes related to war captivity. *Archives of General Psychiatry, 37*, 430-443.

This study was conducted on ex-POWs of the U.S. Air Force who had been shot down over North Vietnam and captured. The results of a questionnaire were compiled to analyze the long-term consequences of a war imprisonment experience. Indications from the study are that individuals who experienced the greatest stress during their captivity believed they gained more psychologically than those who were less stressed.

Solomon, Z., & Dekel, R. (2007). Posttraumatic stress disorder and posttraumatic growth among Israeli ex-POWs. *Journal of Traumatic Stress, 20*, 303-312.

This article presents a study on PTSG and PTG outcomes of the captivity from a sample of former Israeli POWs and non-POWs. The results indicate that former POWS had higher levels of PTSD and PTG than regular combat veterans.

Southwick, S. M., Bremner, J. D., Rasmusson, A., Morgan III, C. A., Arnsten, A. & Charney, D. S. (1999). Role of norephinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological Psychiatry, 46*(9), 1192-1204.

This article describes the functioning of neuropeptide Y within the sympathetic nervous system. NPY helps regulate the optimal activation range of the SNS by off-setting NE levels. Research indicates that high levels of NE can increase anxiety, panic, heart rate, and blood pressure which can be adverse to performance.

Southwick, S. M., Ozbay, F., Charney, D., McEwen, B. S. (2008) Adaptation to Stress and Psychobiological Mechanisms of Resilience. In: B. Lukey, V. Tepe (Eds.). *Biobehavioral Resilience to Stress* (Vol. 1, pp. 91-115). Boca Raton, FL: CRC Press.

This study examines the neurobiological basis for resilience and mechanisms that are associated with the regulation of factors and phenomena that are related to it. The focus however, is constrained to the discussion of relationships between the human brain and behavior in order to guide future theory and research in this area.

Tedeschi, R. G., & Calhoun, L. G. (1996). The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. *Journal of Traumatic Stress, 9*, 455-471.

This study describes the development of the Posttraumatic Growth Inventory. The PTGI is used to assess positive outcomes that are reported by persons who have experienced traumatic events in 5 main factors: New Possibilities, Personal Strength, Spiritual Change, and Appreciation of Life.

Tedeschi, R. G., Park, C. L., & Calhoun, L. G. (1998). *Posttraumatic Growth: Positive Changes in the Aftermath of Crisis*. Mahwah, NJ: Lawrence Erlbaum Associates.

The authors seek to explain the phenomenon of how people undergo positive changes from negative traumatic experiences.

Thorsell, A., Michalkiewicz, M., Dumont, Y., Quirion, R., Caberlotto, L., Rimondini, R., Mathe, A.A., & Heilig, M. (2000). Behavioral insensitivity to restraint stress, absent fear suppression of behavior and impaired spatial learning in transgenic rats with hippocampal neuropeptide Y overexpression. *Proceedings of the National Academy of Sciences of the united States of America, 97*, 12852-12857.

This experiment found that rats with high levels of NPY were resistant to restraint stress and showed less fear-related behavior than control rats.

Thorsell, A., Svennson, P., Wiklund, L., Sommer, W., Ekman, R., & Heilig, M. (1998). Suppresed neuropeptide Y (NPY) mRNA in rat amygdale following restraint stress. *Regulatory Peptides, 75*, 247-254.

This experiment found that restraint stress in rats resulted in the suppression of NPY in the brain.

Yehuda, R., Brand, S., & Yang, R. (2006). Plasma Neuropeptide Y Concentrations in Combat Exposed Veterans: Relationship to Trauma Exposure, Recovery from PTSD, and Coping. *Biological Psychiatry, 59*(7), 660-663.

This study seeks to examine the role of neuropeptide Y as a protective stress factor. Measuring NPY levels in military veterans with combat experience and PTSD, higher NPY levels were found in veterans without PTSD. The research concludes that NPY levels may represent a biologic correlate of resilience to recovery from stressful experiences.

Yerkes, R.M. & Dodson, J.D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology, 18*, 459-482.

This classic experiment found that there is a positive correlation between performance and level of arousal up until a critical point of arousal, at which point the correlation becomes negative.

Zukowska-Grojec, Z. (1995). Neuropeptide Y: a novel sympathetic stress hormone and more. *Annals of the New York Academy of Science, 771*, 219-233.

The authors detail the effects of NPY in relation to stress in the human body.

Zukowska-Grojec, Z., Dayao, E.K., Karwatowska-Prokopczuk, E., Hauser, G.J., & Doods, H.N. (1996). Stress-induced mesenteric vasoconstriction in rats is mediated by neuropeptide Y Y1 receptors. *Heart and Circulatory Physiology, 270 (2), 796-800.*

This experiment found that NPY mitigated the magnitude of vasoconstriction as a result of stress in rats.